REMARKS

The Restriction Requirement

Applicants appreciate the decision by the Office to rejoin Claims 32-34 in the examination of the instant application.

The Amendments to the Claims

Claims 1-55 were pending in the subject application. Claims 5, 7, 8, 14, 24, 27-29 and 50-54 were withdrawn from consideration after the Restriction Requirement in Paper No. 10 was made final. Applicants note that Claim 55 was not included in the listing of withdrawn claims, nor was Claim 55 mentioned in the rejections, and thus applicants request clarification as to the status of Claim 55. Claims 3, 21 and 25 have been cancelled, without prejudice to pursue the subject matter of these claims in other applications. Claims 1, 2, 4, 6, 9-13, 15-20, 22, 23, 26, 30-34 and 55, are now pending and being examined.

Claim 1, 4, 19, 22, 23 and 26, have been amended to clarify the invention. Support for the amendments to these claims can be found on page 10, lines 5-10, page 13, lines 29-31 through page 14, lines 1-2; page 18, lines 20-23; Example VI, pages 37-38, and the original claims as filed.

Claim 32 has been amended to clarify the invention. Support for the amendment to Claim 32 can be found on page 10, lines 5-10; page 12, lines 19-31 through page 13, lines 1-22; page 13, lines 29-31; page 14, lines 6-15; page 15, lines 9-16; page 19, lines 18-25; and the original claims as filed.

No new matter has been added by these amendments. Entry of these claims is respectfully requested.

Reconsideration and withdrawal of the objections and rejections of the claims are respectfully requested in view of the above-amendments and remarks that follow.

Priority

The Patent Office indicates that the originally-filed specification does not contain language claiming priority of a prior-filed application. In response, Applicants have amended the specification to claim priority of a prior-filed U.S. provisional application and a prior-filed international application.

In accordance with 37 C.F.R. §1.78(a)(2)(iii), Applicants may amend the specification of the subject application to claim priority of the prior-filed international application, PCT/US00/00179, because the subject application is a non-provisional application that was filed with an application data sheet claiming priority of PCT/US00/00179. A copy of the originally-filed application data sheet from the subject application is attached herein as Exhibit 1.

Additionally, in accordance with 37 C.F.R. §1.78(5)(ii)(B), Applicants may amend the specification to claim priority of the prior-filed provisional application, U.S. Serial No. 60/114,795, because the subject application entered national stage from an international application that was filed before November 29, 2000. A copy of the originally-filed return postcard from PCT/US00/00179, date stamped by the U.S. Patent and Trademark Office is attached herein as Exhibit 2.

THE REJECTIONS UNDER 35 U.S.C. §102

The Patent Office rejected claims 1-3, 4, 6, 9-13, 15-17, 21-23, 25, 26 and 31-34 under 35 U.S.C. §102(b), as allegedly anticipated by Peters et al., and evidenced by Moll et al.

In the rejection, the Office asserts that Peters et al. disclose the administration of an ACE inhibitor and an Ang II receptor blocker to animal models of renal disease; that both inhibit TGFβ activity; "overproduction of TGFβ leads to matrix accumulation and tissue fibrosis; TGFβ over expression causes increased synthesis of matrix proteins, causes decreased degradation of matrix proteins by suppression of protease expression and increased expression of protease inhibitors such as TMP (a metalloproteinase inhibitor." (Office Action, Page 5).

Applicants traverse the rejection. Applicants respectfully contend that the Patent Office improperly rejected claims 1-3, 4, 6, 9-13, 15-17, 22, 23, 26 and 31-34 under 35 U.S.C. §102(b).

Peters does not disclose each and every element of the claimed invention.

The Standard for Novelty

A claimed invention is anticipated if each and every element of the claimed invention is disclosed in a single prior art reference in a manner sufficient to enable one skilled in the art to reduce the invention to practice, thus placing the invention in possession of the public. W.L. Gore & Assocs., Inc. v. Garlock, Inc., 220 U.S.P.Q. 303 (Fed. Cir. 1983), *cert. Denied* 469 U.S. 851 (1984); In re Donohue, 226 U.S.P.Q. 619 (Fed. Cir. 1985); Scripps Clinic & Research Found. V. Genentech, Inc., 927 F. 2d 1565, 1576-7 (Fed. Cir.), clarified, on recons., 1991 U.S. App. LEXIS 33,486 (Fed. Cir. 1991).

The claimed invention must be *identically* disclosed within the four corners of one, and only one, piece of prior art, Scripps Clinic & Research Found. V. Genentech, Inc., 927 F. 2d 1565, 176 (Fed. Cir. 1991). The absence of even a single element from a prior art reference negates anticipation. Atlas Powder Co. v. E. I. Du Pont de Nemours & Co., 750 F. 2d 1569, 1574 (Fed. Cir. 1984).

Peters et al. is an article co-authored by the present inventors. The study reported in that article demonstrated that "TGF-β overexpression and fibrotic disease were reduced more effectively at doses of enalapril and losartan that are higher than those known to reduce blood pressure. Enalapril and losartan are equipotent at maximally effective doses and combined therapy yields no additional effect." (page 1578, column 2). Moreover, the authors concluded that "neither ACE inhibition nor Ang II type receptor antagonism will be sufficient to normalize over-production of TGF-β." (Id.). The authors end by suggesting that "it is likely that they must be combined with other agents which act through different mechanisms, in order to ultimately stop disease." (Id.)

Moll et al. reported that levels of TGF-β1 and PAI-1 mRNA levels correlated with the severity of glomerular lesions, suggesting that a perturbation of the PA/PAI balance caused by induction of PAI-1 gene expression mediated by TGF-β1, may play a role in the progression of glomerular lesions. The authors cited references disclosing that TGF-β1 decreases the synthesis of proteases and induces the production of PAI1. (page 1459, column 2).

Contrary to the assertions of the Office, neither Peters et al., or Moll et al., anticipate the invention recited in the claims of the instant application.

The inventors of the invention recited in the present claims have made a number of pioneering discoveries relating to the role of TGFβ in fibrotic disease, and the effects of agents that inhibit TGFβ on accumulation of extracellular matrix. Applicants are coauthors on the Peters et al reference cited by the Examiner. At the time of the study reported in Peters et al., it was known that administration of an anti-TGFβ agent at maximal dose could only provide approximately 50% reduction in a number of measures of fibrotic disease, including extracellular matrix accumulation. Applicants were interested in exploring how to achieve optimal decrease in ECM accumulation and thus

anti-fibrotic therapeutic effects. In the study reported in Peters et al., the inventors were surprised to obtain results that indicated that combinations of a class of anti-hypertensive agents (angiotensin II blockers) known to have an anti-fibrotic effect at maximal doses, showed no additional therapeutic effect when combined, i.e. there was no additional reduction in measures of fibrotic disease, including extracellular matrix accumulation, by combining these agents that act by similar mechanisms.

Peters et al. does not describe or suggest describe or suggest the use of "a first agent that inhibits TGFß- associated accumulation of extracellular matrix," and a "second agent that inhibits TGFß-associated accumulation of extracellular matrix, such that the combination of the first and second agent results in greater reduction in accumulation of excess extracellular matrix than either agent does alone."

In Peters et al, the combination of agents did not result in an increased reduction in accumulation of excess extracellular matrix, as compared to the effects of either agent alone on extracellular matrix accumulation. Peters et al. also do not describe or suggest the combination of an agent that reduces TGFβ-associated accumulation of extracellular matrix, with a different, second agent that causes enhanced degradation of excess accumulated matrix. The suggestion in Peters et al. to use agents that act by other mechanisms, as well as losartan and enalapril, was an "invitation for further experimentation." Peters et al. do not disclose "each and every element," of the present claims, as required for anticipation.

Similarly, Moll et al. do not disclose the use of an agent that inhibits TGFß-associated accumulation of extracellular matrix, and a second agent that inhibits TGFß-associated accumulation of extracellular matrix, such that the combination of the first and second agent results in greater inhibition of accumulation of matrix than either agent does alone. Moll et al. also do not describe or suggest the combination of an agent that reduces TGFβ-associated accumulation of extracellular matrix, with a different, second agent that

causes enhanced degradation of excess accumulated matrix, to inhibit TGFβ and degrade extracellular matrix. Moll et al. simply reference that TGF-β1 decreases the synthesis of proteases and induces the production of PAI1, but do not suggest the use of an agent, such as a protease, to degrade extracellular matrix, in combination with an anti-TGFβ agent. Nor do Moll et al. suggest the use of an anti-TGFβ agent to increase the amount of protease present in fibrotic conditions.

Applicants thus respectfully assert that the rejection of claims under 35 U.S.C. §102(b), has been overcome, and should be withdrawn.

THE REJECTION UNDER 35 U.S.C. § 103

Claims 10 and 30 were rejected under 35 U.S.C. §103 based on Peters et al. in combination with Border et al. (W0 96/2518). The Office asserted that Peters et al. shows "that TGFβ inhibitors acts as ECM degradation agents and also to show that there is motivation to combine TGFβ inhibitors in a treatment." (Office Action, page 6). The Office states that Border et al. teach "the use of nucleic acids to express desired TGFβ inhibitors in a treatment, for example." (Office Action, page 6). The Office argues further that "it is prima facie obvious to combine equivalents known for the same purpose, therefore one in the art would clearly have known to combine the administration of nucleic acids encoding TFGβ inhibitors such as antibodies, decorin, etc." (Office Action, page 6).

The Legal Standards for Establishing Obviousness Under 35 U.S.C. §103

As stated in MPEP §2142, three (3) criteria must be met to establish a *prima facie* case of obviousness:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based upon applicants' disclosure.[1]

The teaching or suggestion to make the claimed combination, and the reasonable expectation of success, must both be found in the prior art, not in the Applicant's disclosure (In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)).

Obviousness is a question of law based on findings of underlying facts relating to the prior art, the skill of the artisan, and objective considerations. See Graham v. John Deere Co., 383 U.S. 1, 17, 148 USPQ 459, 467 (1966). To establish a prima facie case of obviousness based on a combination of the content of various references, there must be some teaching, suggestion or motivation in the prior art to make the specific combination that was made by the applicant. In re Raynes, 7 F.3d 1037, 1039, 28 USPQ2d 1630, 1631 (Fed. Cir. 1993); In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992). Obviousness can not be established by hindsight combination to produce the claimed invention. In re Gorman, 933 F.2d 982, 986, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991). As discussed in Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1143, 227 USPQ 543, 551 (Fed. Cir. 1985), it is the prior art itself, and not the applicant's achievement, that must establish the obviousness of the combination.

The teachings of the references, their relatedness to the field of the applicant's endeavor, and the knowledge of persons of ordinary skill in the field of the invention, are all relevant considerations. See In re Oetiker, 977 F.2d at 1447, 24 USPQ2d at 1445-46; In

[1] MPEP §2142, *citing In re Vaeck,* 957 F . 2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

re Gorman, 933 F.2d at 986-87, 18 USPQ2d at 1888; In re Young, 927 F.2d 588, 591, 18 USPQ2d 1089, 1091 (Fed. Cir. 1991). When the references are in the same field as that of the applicant's invention, knowledge thereof is presumed. However, the test of whether it would have been obvious to select specific teachings and combine them, as did the applicant, must still be met by identification of some suggestion, teaching, or motivation in the prior art, arising from what the prior art would have taught a person of ordinary skill in the field of the invention. In re Fine, 837 F.2d 1071, 1075, 5 USPQ2d 1596,1600 (Fed. Cir. 1988).

The Examiner Has Not Established A *Prima Facie* Case Of Obviousness

The Examiner has not established a *prima facie* case of obviousness because none of the three necessary criteria for obviousness under 35 U.S.C. §103 have been met.

Peters et al., alone, or in combination with Border et al., do not teach or suggest the use of agents that reduce TGFβ-associated accumulation of extracellular matrix, in combination with different agents that cause enhanced degradation of excess accumulated matrix, as recited in the present claims, as amended. Peters et al. also do not teach or suggest the use of combinations of agents that reduce TGFβ-associated accumulation of extracellular matrix, where the combination of agents results in greater reduction of extracellular matrix accumulation than by any single agent alone. Moreover, Peters et al. teach away from use of a combination of anti-TGFβ agents in that the combination of losartan and enalapril, at maximal doses did not result in an additive therapeutic effect. Thus, the Office's statement that it is obvious to "combine equivalents known for the same purpose," is controverted by the Peters et al. disclosure.

Contrary to the assertions of the Office, Peters et al. do not disclose "that TGFβ inhibitors acts as ECM degradation agents," because the use of TGFβ inhibitors, or any other agents for ECM degradation, is not disclosed or suggested in Peters et al. As discussed above,

Peters et al. do not motivate combination of "TGFβ inhibitors in a treatment," because the results obtained by Peters et al. from combination of two TGFβ inhibiting agents (the antihypertensives, losartan and enalapril) did not result in enhanced therapeutic effect (ie reduction in excess extracellular matrix accumulation), beyond results obtained by each agent used alone.

The Office also stated that Border et al. teach "the use of nucleic acids to express desired TGFβ inhibitors in a treatment, for example." (Office Action, page 6). Border et al. do not describe or suggest the use of nucleic acids expressing a combination of TGFβ inhibitors, let alone the combination of agents for reducing TGFβ associated accumulation of excess extracellular matrix with agents for degrading extracellular matrix.

Therefore, Peters et al., alone or in combination with Border et al., do not render the invention of the present claims obvious.

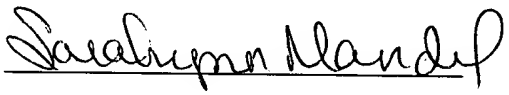
Therefore, the cited references do not render the present invention obvious under 35 U.S.C. 103, and this rejection of Claims 10 and 30 should be withdrawn.

CONCLUSION

Applicant believes that the amendments and remarks provided herein, address all of the issues raised by the Examiner. Accordingly, Applicant believes that all grounds for rejection of the claims have been successfully overcome, and that all the claims are in condition for allowance. Withdrawal of the rejections, is requested, and prompt allowance of the claims is solicited. If any issues remain in connection with the claims, the Examiner is requested to contact the undersigned by telephone, to discuss the same.

No fee is deemed necessary in connection with the filing of this Amendment. If any additional fees are necessary, the Patent Office is authorized to charge the additional fee to Deposit Account No. 50-0306.

Respectfully submitted,



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